AMENDMENTS TO THE SPECIFICATION

Please amend the specification as shown:

Please delete paragraph [0023] on page 11, lines 1-6, and replace it with the following paragraph:

Fig. 3 shows a BLAST analysis of rat endomannosidase to identify homologues. Panel **A** shows identification of a human sequence **(SEQ ID NO: 24)** showing 88% identity to the C-terminus of rat endomannosidase **(SEQ ID NO: 23)**. Panel **B** (residues 1-23 of **SEQ ID NO: 24**, aligned with residues 173-195 of **SEQ ID NO: 25**, respectively in order of appearance), shows the N-terminus of isolated sequence from Panel **A** which was used to isolate the 5' region of the human endomannosidase in Panel **C**. Panel **C** shows sequence of the potential N-terminus of human endomannosidase **(SEQ ID NO: 25)**.

Please delete paragraph [0024] on page 11, lines 7-15, and replace it with the following paragraph:

Fig. 4 shows nucleotide and amino acid sequences of human liver endomannosidase. Nucleotide sequence (*upper*) **(SEQ ID NO: 1)** and one-letter amino acid sequence (*lower*) **(SEQ ID NO: 2)** of human endomannosidase are shown with residue numbers labeled on the left. The nucleotide region in bold represents the overlapping segments of Genbank sequences gi: 18031878 (*underlined*) and gi: 20547442 (*regular text*) used to assemble the putative full-length human liver endomannosidase. The putative transmembrane domain identified by Kyte and Doolittle analysis (*J. Mol. Biol.* 157: 105-132 (1982)) (see **Fig. 5**) is highlighted by an open box.

Please delete paragraph [0026] on page 11, lines 22-27, and replace it with the following paragraph:

Fig. 6 shows nucleotide and amino acid sequences of mouse endomannosidase (Genbank AK030141). Nucleotide sequence (*upper*) **(SEQ ID NO: 3)** and one-letter amino acid sequence (*lower*) **(SEQ ID NO: 4)** of mouse endomannosidase are shown with residue numbers labeled on the left. The putative transmembrane domain identified by Kyte and Doolittle analysis (*J. Mol. Biol.* 157: 105-132 (1982)) is highlighted by an open box.

Please delete paragraph [0027] on page 11, line 28, to page 12, line 2, and replace it with the following paragraph:

Fig. 7 shows the alignment of three endomannosidase open-reading frames. The human **(SEQ ID NO: 2)**, mouse **(SEQ ID NO: 4)**, and rat **(SEQ ID NO: 26)** endomannosidase ORFs were aligned using the Megalign software of the DNASTAR suite of programs. The algorithm chosen for the analysis was the CLUSTAL V version (Higgins and Sharp *Comput. Appl. Biosci.* 5, 151-153 (1989)). Residues displayed by shading represent amino acids that are identical between at least two of the ORFs. The amino acid position of each ORF is presented to the left of the aligned sequence.

Please delete paragraph [0087] on page 28, lines 12-27, and replace it with the following paragraph:

The rat endomannosidase has been cloned (Spiro et al., *J. Biol. Chem.* 272(46):29356-29363 (1997)). Although the rat endomannosidase is the only cloned member of this family to date, genes and ESTs that show significant homology to this ORF, and in particular to the rat endomannosidase catalytic domain, are in databases. By performing a protein BLAST search using the rat endomannosidase protein sequence (Genbank gi:2642187) we identified two hypothetical human proteins in Genbank having regions of significant homology with the rat endomannosidase sequence (**Example 2; Figs. 3A-C**). Combining 5' and 3' regions of these two hypothetical proteins into one ORF produced a putative sequence of 462 amino acids (**Fig. 4**) and a predicted molecular mass of 54 kDa. Alignment of this putative human endomannosidase sequence to the known rat sequence indicated that the C-termini of these proteins are highly conserved but that the N-termini are more varied (**Fig. 7**). It is likely that the conserved region (i.e., from the motif 'DFQ(K/R)SDRIN' **(SEQ ID NO: 27)** to the C-terminus), corresponds to the catalytic domain in each endomannosidase, or at least to a region essential for activity.

Please delete paragraph [0088] on page 28, line 28, to page 29, line 9, and replace it with the following paragraph:

Based on the above-deduced human endomannosidase gene sequence, we constructed primers and amplified an open reading frame (ORF) from a human liver cDNA library by PCR (**Example 2**). The nucleic acid sequence which

encodes that ORF is 77.8% identical across its length to the full-length nucleic acid sequence encoding the rat endomannosidase ORF (sequence pair distances using the Clustal methods with weighted residue weight table). At the amino acid sequence level, the human and rat endomannosidase proteins are predicted to be 76.7% identical overall. In the more conserved region noted above (i.e., from the motif 'DFQ(K/R)SDRIN' **(SEQ ID NO: 27)** to the C-terminus), the proteins are 86.6% identical overall. Unlike the rat protein, the predicted human protein has a very hydrophobic region at the N-terminus (residues 10-26) which may be a transmembrane region (**Fig. 4**, boxed). The human endomannosidase (unlike the rat protein), is predicted to be a type-II membrane protein, as are most other higher eukaryotic mannosidases.

Please delete paragraph [0100] on page 33, lines 4-15, and replace it with the following paragraph:

The mouse ORF shows substantial homology to the known rat endomannosidase and the human liver endomannosidase of the present invention (**Fig. 7**). Specifically, the nucleic acid sequence which encodes the mouse endomannosidase ORF is 86.0% and 84.2% identical across its length to the full-length nucleic acid sequence encoding the rat and the human endomannosidase ORFs, respectively (sequence pair distances using the Clustal methods with weighted residue w~~i~~eight table). At the amino acid sequence level, the mouse and rat endomannosidase proteins are predicted to be 82.3% identical, a~~n~~nd the mouse and human endomannosidase proteins are predicted to be 84.9% identical overall. In

the more conserved region noted above (i.e., from the motif 'DFQ(K/R)SDRIN' **(SEQ ID NO: 27)** to the C-terminus), the mouse and rat proteins are 92.3% identical, and the mouse and human proteins are 86.1% identical, overall.

Please delete paragraph [0110] on page 35, line 31, to page 36, line 16, and replace it with the following paragraph:

The human liver endomannosidase and the putative mouse endomannosidase are the second and third members of a newly developing family of glycosidic enzymes, with the rat endomannosidase enzyme being the first such member. Sequence comparison of the human, mouse and rat ORFs (**Fig.7**) demonstrates high homology from the motif 'DFQ(K/R)SDRI' (residues 1-8 of **SEQ ID NO: 27**) to the C-termini of the sequences suggesting that this region encodes an essential fragment of the protein, and potentially, the catalytic domain. In contrast, the lower homology within the N-termini of the proteins demonstrates evolutionary divergence. Like the majority of glycosidases and glycosyltransferases, the mouse and human enzymes have a hydrophobic region indicative of a transmembrane domain. Such a domain would facilitate the orientation and localization of the enzyme in the secretory pathway. In contrast, the rat endomannosidase does not have a transmembrane domain but does have a glycine residue at position 2 (Spiro 1997, *supra*). This penultimate glycine residue has the potential to be myristoylated, which in turn provides a mechanism for membrane localization (Boutin, *Cell Signal* 9: 15-35 (1997)). Alternatively, myristoylation may not be the means of rat endomannosidase localization to the Golgi

(Zuber 2000, *supra*) -- protein-protein interactions may be the determining mechanism.

Please delete paragraph [0120] on page 40, lines 2-12, and replace it with the following paragraph:

Another useful sub-library includes nucleic acid sequences encoding targeting signal peptides that result in localization of a protein to a particular location within the ER, Golgi, or trans Golgi network. These targeting peptides may be selected from the host organism to be engineered as well as from other related or unrelated organisms. Generally such sequences fall into three categories: (1) N-terminal sequences encoding a cytosolic tail (ct), a transmembrane domain(tmd) and part or all of a stem region (sr), which together or individually anchor proteins to the inner (luminal) membrane of the Golgi; (2) retrieval signals which are generally found at the C-terminus such as the HDEL **(SEQ ID NO: 28)** or KDEL **(SEQ ID NO: 29)** tetrapeptide; and (3) membrane spanning regions from various proteins, e.g., nucleotide sugar transporters, which are known to localize in the Golgi.

Please delete paragraph [0122] on page 40, lines 23-29, and replace it with the following paragraph:

Still other useful sources of targeting peptide sequences include retrieval signal peptides, e.g. the tetrapeptides HDEL **(SEQ ID NO: 28; also shown in column 1 of Table 1)** or KDEL **(SEQ ID NO: 29)**, which are typically

found at the C-terminus of proteins that are transported retrograde into the ER or Golgi. Still other sources of targeting peptide sequences include (a) type II membrane proteins, (b) the enzymes with optimum pH, (c) membrane spanning nucleotide sugar transporters that are localized in the Golgi, and (d) sequences referenced in **Table 1**.